The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in September 2011.

HUMALOG MIX 25 & HUMALOG MIX 50 KwikPen

1. NAME OF THE MEDICINAL PRODUCT

Humalog Mix25 100 U/ml KwikPen, suspension for injection

Humalog Mix50 100U/ml KwikPen, suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Humalog Mix is a white, sterile suspension

2.2 Qualitative and quantitative composition

One ml contains 100U (equivalent to 3.5mg) insulin lispro (recombinant DNA origin produced in E.coli). Each container includes 3ml equivalent to 300U insulin lispro.

Humalog Mix25 consists of 25% insulin lispro solution and 75% insulin lispro protamine suspension.
Humalog Mix50 consists of 50% insulin lispro solution and 50% insulin lispro protamine suspension.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Humalog Mix25 and Humalog Mix50 are indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

4.2 Posology and method of administration

The dosage should be determined by the physician, according to the requirement of the patient.

Humalog Mix25 or Humalog Mix50 may be given shortly before meals. When necessary, Humalog Mix25 or Humalog Mix50 can be given soon after meals. Humalog Mix25 or Humalog Mix50 should only be given

by subcutaneous injection. Under no circumstances should Humalog Mix25 or Humalog Mix50 be given intravenously.

Subcutaneous administration should be in the upper arms, thighs, buttocks, or abdomen. Use of injection sites should be rotated so that the same site is not used more than approximately once a month.

When administered subcutaneously care should be taken when injecting Humalog Mix25 or Humalog Mix50 to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use the proper injection techniques.

The rapid onset and early peak of activity of Humalog itself is observed following the subcutaneous administration of Humalog Mix25 or Humalog Mix50. This allows Humalog Mix25 or Humalog Mix50 to be given very close to mealtime.

The duration of action of the insulin lispro protamine suspension (BASAL) component of Humalog Mix 25 or Humalog Mix50 is similar to that of a basal insulin (NPH).

The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the duration of action of Humalog Mix25 or Humalog Mix50 is dependent on dose, site of injection, blood supply, temperature, and physical activity.

4.3 Contraindications

Hypersensitivity to insulin lispro or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Under no circumstances should Humalog Mix25 or Humalog Mix50 be given intravenously.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal, human, human insulin analogue), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease or medications such as beta-blockers.

A few patients who have experienced hypoglycaemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin. Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

The use of dosages which are inadequate or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Insulin requirements may be reduced in the presence of renal impairment. Insulin requirements may be reduced in patients with hepatic impairment due to reduced capacity for gluconeogenesis and reduced

insulin breakdown; however, in patients with chronic hepatic impairment, an increase in insulin resistance may lead to increased insulin requirements.

Insulin requirements may be increased during illness or emotional disturbances.

Adjustment of dosage may also be necessary if patients undertake increased physical activity or change their usual diet. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

Administration of insulin lispro to children below 12 years of age should be considered only in case of an expected benefit when compared to regular insulin.

Combination of Humalog Mix25 with pioglitazone:
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind, if treatment with the combination of pioglitazone and Humalog Mix is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued, if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Insulin requirements may be increased by substances with hyperglycaemic activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy, danazol, $beta_2$ stimulants (such as ritodrine, salbutamol, terbutaline).

Insulin requirements may be reduced in the presence of substances with hypoglycaemic activity, such as oral hypoglycaemics, salicylates (for example, acetylsalicylic acid), sulpha antibiotics, certain antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors), certain angiotensin converting enzyme inhibitors (captopril, enalapril), angiotensin II receptor blockers, beta-blockers, octreotide or alcohol.

Mixing Humalog Mix 25 or Humalog Mix50 with other insulins has not been studied.

The physician should be consulted when using other medications in addition to Humalog Mix25 or Humalog Mix50 KwikPen (see section 4.4).

4.6 Fertility, pregnancy and lactation

Data on a large number of exposed pregnancies do not indicate any adverse effect of insulin lispro on pregnancy or on the health of the foetus/newborn.

It is essential to maintain good control of the insulin-treated (insulin-dependent or gestational diabetes) patient throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as well as general health, is essential in pregnant patients with diabetes.

Patients with diabetes who are breast-feeding may require adjustments in insulin dose, diet or both.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving, this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia is a result of both the insulin dose and other factors e.g. a patient`s level of diet and exercise.

Local allergy in patients is common (1/100 to <1/10). Redness, swelling, and itching can occur at the site of insulin injection. This condition usually resolves in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. Systemic allergy, which is rare (1/10,000 to <1/1,000) but potentially more serious, is a generalised allergy to insulin. It may cause a rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalised allergy may be life-threatening.

Lipodystrophy at the injection site is uncommon (1/1,000 to <1/100).

Cases of oedema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy.

4.9 Overdose

Insulins have no specific overdose definitions because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability and other metabolic processes. Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

Hypoglycaemia may be associated with listlessness, confusion, palpitations, headache, sweating and vomiting.

Mild hypoglycaemic episodes will respond to oral administration of glucose or other sugar or saccharated products.

Correction of moderately severe hypoglycaemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously.

If the patient is comatose, glucagon should be administered intramuscularly or subcutaneously. However, glucose solution must be given intravenously if glucagon is not available or if the patient fails to respond to glucagon. The patient should be given a meal as soon as consciousness is recovered.

Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group:
Humalog Mix25 and Humalog Mix50 are premixed suspensions consisting of insulin lispro (fast-acting human insulin analogue) and insulin lispro protamine suspension (intermediate acting human insulin analogue). ATC Code: A10A D04.

The primary activity of insulin lispro is the regulation of glucose metabolism.

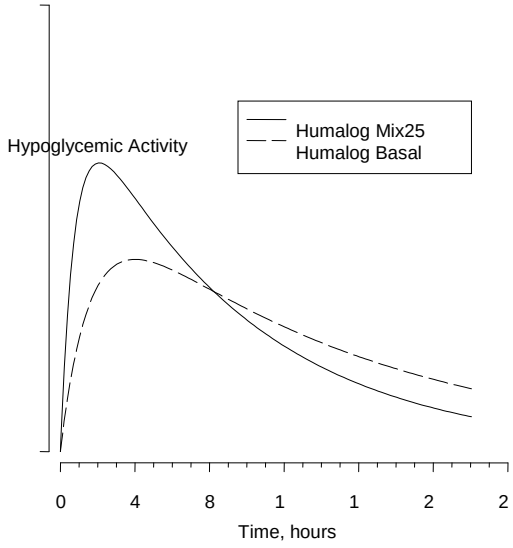
In addition, insulins have several anabolic and anti-catabolic actions on a variety of different tissues. Within muscle tissue this includes increasing glycogen, fatty acid, glycerol and protein synthesis and amino acid uptake, while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

Insulin lispro has a rapid onset of action (approximately 15 minutes), thus allowing it to be given closer to a meal (within zero to 15 minutes of the meal) when compared to regular insulin (30 to 45 minutes before). The rapid onset and early peak of activity of insulin lispro is observed following the subcutaneous administration of Humalog Mix25 or Humalog Mix50. Humalog BASAL has an activity profile that is very similar to that of a basal insulin (NPH) over a period of approximately 15 hours.

Clinical trials in patients with type 1 and type 2 diabetes have demonstrated reduced postprandial hyperglycaemia with Humalog Mix25 compared to human insulin mixture 30/70. In one clinical study there was a small (0.38 mmol/l) increase in blood glucose levels at night (3a.m.).

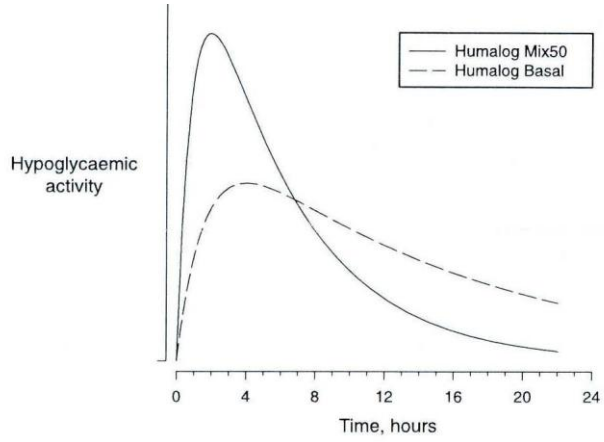
In the figure below the pharmacodynamics of Humalog Mix25 and BASAL are illustrated.

Hypoglycaemic activity



Time(hours)

In the figure below the pharmacodynamics of Humalog Mix50 and BASAL are illustrated.



The above representations reflect the relative amount of glucose over time required to maintain the subject's whole blood glucose concentrations near fasting levels and is an indicator of the effect of these insulins on glucose metabolism over time.

The glucodynamic response to insulin lispro is not affected by renal or hepatic function impairment. Glucodynamic differences between insulin lispro and soluble human insulin, as measured during a glucose clamp procedure, were maintained over a wide range of renal function.

Insulin lispro has been shown to be equipotent to human insulin on a molar basis but its effect is more rapid and of a shorter duration.

In two 8-month open label crossover studies, type 2 diabetes patients who were either new to insulin therapy or already using one or two injections of insulin, received 4 months of treatment with Humalog Mix25 (used twice daily with metformin) and insulin glargine (used once daily with metformin) in a randomised sequence. Detailed information can be found in the following table.

	Insulin-Naive Patients n = 78	**Not Insulin-Naive Patients** n = 97
Mean total daily insulin dose at endpoint	0.63 U/kg	0.42 U/kg
Haemoglobin A1c –Reduction[1]	1.30% (mean at baseline = 8.7%)	1.00 % (mean at baseline = 8.5%)
Reduction of the mean of combined morning / evening two-hour postprandial blood glucose[1]	3.46 mM	2.48 mM
Reduction of the mean fasting blood glucose[1]	0.55 mM	0.65 mM
Incidence of hypoglycaemia at endpoint	25%	25%
Bodyweight gain[2]	2.33 kg	0.96 kg

[1] from baseline to end of Humalog Mix25 treatment
[2] in patients randomised to Humalog Mix25 during the first crossover period

5.2 Pharmacokinetic properties

The pharmacokinetics of insulin lispro reflect a compound that is rapidly absorbed, and achieves peak blood levels 30 to 70 minutes following subcutaneous injection. The pharmacokinetics of insulin lispro protamine suspension are consistent with those of an intermediate acting insulin such as NPH. The pharmacokinetics of Humalog Mix25 and Humalog Mix50 are representatives of the individual pharmacokinetic properties of the two components. When considering the clinical relevance of these kinetics, it is more appropriate to examine the glucose utilisation curves (as discussed in 5.1).

Insulin lispro maintains more rapid absorption when compared to soluble human insulin in patients with renal impairment. In patients with type 2 diabetes over a wide range of renal function the pharmacokinetic differences between insulin lispro and soluble human insulin were generally maintained and shown to be independent of renal function. Insulin lispro maintains more rapid absorption and elimination when compared to soluble human insulin in patients with hepatic impairment.

5.3 Preclinical safety data

In *in vitro* tests, including binding to insulin receptor sites and effects on growing cells, insulin lispro behaved in a manner that closely resembled human insulin. Studies also demonstrate that the dissociation of binding to the insulin receptor of insulin lispro is equivalent to human insulin. Acute, one month and twelve month toxicology studies produced no significant toxicity findings.

Insulin lispro did not induce fertility impairment, embryotoxicity or teratogenicity in animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Humalog Mix25
Protamine sulphate, *meta*Cresol [1.76 mg/ml], liquefied phenol [0.80 mg/ml], glycerol, dibasic sodium phosphate, zinc oxide, water for injections. Hydrochloric acid and sodium hydroxide may have been used to adjust pH to 7.0-7.8.

Humalog Mix50
Protamine sulphate, metaCresol [2.20 mg/ml], liquefied phenol [1.00 mg/ml], glycerol, dibasic sodium phosphate, zinc oxide, water for injections. Hydrochloric acid and sodium hydroxide may have been used to adjust pH to 7.0-7.8.

6.2 Incompatibilities

Mixing Humalog Mix25 or Humalog Mix50 with other insulins has not been studied. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unused pre-filled pens
3 years.

After first use
28 days.

6.4 Special precautions for storage

Unused pre-filled pens
Store in a refrigerator (2°C - 8°C). Do not freeze. Do not expose to excessive heat or direct sunlight.

After first use
Store below 30°C. Do not refrigerate. The pre-filled pen should not be stored with the needle attached.

6.5 Nature and contents of container and special equipment for use, administration or implantation

The suspension is contained in type I flint glass cartridges, sealed with halobutyl disc seals and plunger heads and secured with aluminium seals. Dimeticone or silicone emulsion may have been used to treat the cartridge plunger, and/or the glass cartridge. The 3 ml cartridges are sealed in a disposable pen injector, called the "KwikPen". Needles are not included.

Not all packs may be marketed.

5 x 3 ml Humalog Mix25 100 U/ml KwikPens.
5 x 3 ml Humalog Mix50 100U/ml KwikPens.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling

The KwikPen should be rotated in the palms of the hands ten times and inverted 180° ten times immediately before use to resuspend the insulin until it appears uniformly cloudy or milky. If not, repeat the above procedure until contents are mixed. Cartridges contain a small glass bead to assist mixing. Do not shake vigorously as this may cause frothing which may interfere with the correct measurement of the dose.

The cartridges should be examined frequently and should not be used if clumps of material are present or if solid white particles stick to the bottom or wall of the cartridge, giving a frosted appearance.

Handling of the pre-filled pen
Before using the KwikPen the user manual included in the package leaflet must be read carefully. The KwikPen has to be used as recommended in the user manual.

7. MANUFACTURER:

Lilly France, S.A.S F-67640 Fegersheim, France

8. LICENSE HOLDER

Eli Lilly Israel Ltd P.O.Box 2160, Herzliya Pituach 46120

X KMIX 02